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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	4	OCT 28	KOREAPAT now available on STN
NEWS	5	NOV 30	PHAR reloaded with additional data
NEWS	6	DEC 01	LISA now available on STN
NEWS	7	DEC 09	12 databases to be removed from STN on December 31, 2004
NEWS	8	DEC 15	MEDLINE update schedule for December 2004
NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	JAN 11	CA/CAPLUS - Expanded patent coverage to include Russia (Federal Institute of Industrial Property)

NEWS EXPRESS	JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:25:29 ON 25 JAN 2005

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 15:25:49 ON 25 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0
DICTIONARY FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0

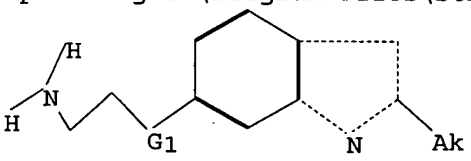
TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

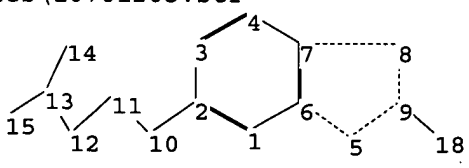
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10761265.str





chain nodes :
10 11 12 13 14 15 18
ring nodes :
1 2 3 4 5 6 7 8 9
chain bonds :
2-10 9-18 10-11 11-12 12-13 13-14 13-15
ring bonds :

```
1-2  1-6  2-3  3-4  4-7  5-6  5-9  6-7  7-8  8-9
exact/norm bonds :
2-10  5-6  5-9  7-8  8-9  9-18  10-11  12-13
exact bonds :
11-12  13-14  13-15
normalized bonds :
1-2  1-6  2-3  3-4  4-7  6-7
isolated ring systems :
containing 1 :


G1:O,S,N,CH2

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  18:CLASS



L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1                STR
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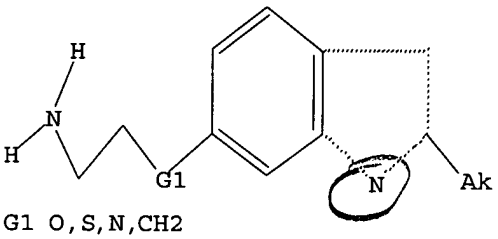


```
G1 O,S,N,CH2
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Structure attributes must be viewed using STN Express query preparation.


=> s l1
SAMPLE SEARCH INITIATED 15:26:05 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  10146 TO ITERATE

  9.9% PROCESSED    1000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       196885 TO   208955
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 15:26:11 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 201259 TO ITERATE

100.0% PROCESSED  201259 ITERATIONS                             13 ANSWERS
SEARCH TIME: 00.00.11
```

L3 13 SEA SSS FUL L1

=> FIL CAPLUS
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	161.33	161.54

FILE 'CAPLUS' ENTERED AT 15:26:26 ON 25 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 25 Jan 2005 VOL 142 ISS 5
FILE LAST UPDATED: 24 Jan 2005 (20050124/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 8 L3

=> s l4 and py<=2000
20649267 PY<=2000
L5 5 L4 AND PY<=2000

=> d l4 ibib abs hitstr tot

L4 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:332162 CAPLUS
DOCUMENT NUMBER: 136:355158
TITLE: Preparation of carboxamides as NMDA receptor antagonists
INVENTOR(S): Horvath, Csilla; Farkas, Sandor; Domany, Gyoergy; Borza, Istvan; Bartane Szalai, Gizella; Nagy, Jozsef; Kolok, Sandor
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

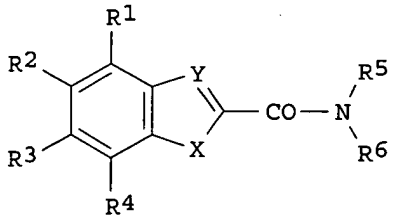
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034718	A1	20020502	WO 2001-HU99	20011015

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002010782	A5	20020506	AU 2002-10782	20011015
EP 1328514	A1	20030723	EP 2001-978687	20011015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004512324	T2	20040422	JP 2002-537711	20011015
US 2003199552	A1	20031023	US 2003-412977	20030411
PRIORITY APPLN. INFO.:			HU 2000-4123 A	20001024
			WO 2001-HU99 W	20011015

OTHER SOURCE(S): MARPAT 136:355158
GI



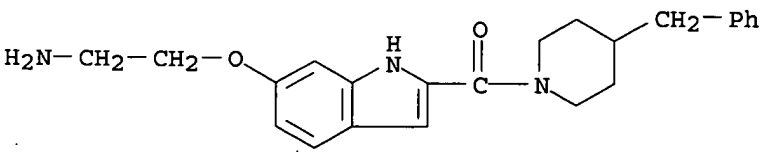
I

AB The title compds. [I; R1-R4 = H, halo, OH, etc,; two of neighboring R1-R4 groups together with one or more identical or different addnl. heteroatom and CH and/or CH2 groups can form 4-7 membered homo- or heterocyclic ring; one of R5 and R6 = H and the other = phenylcyclohexyl, alkyl; or NR5R6 = (un)substituted (un)saturated 4-6 membered heterocyclic ring; X, Y = O, N, S, CH, etc.] were prepared and formulated. Thus, reacting 5-hydroxyindole-2-carboxylic acid with 4-benzylpiperidine in the presence of Et3N and HBTU in MeCN afforded 31% I [X = NH; Y = CH; R1, R3, R4 = H; R2 = OH; NR5R6 = 4-benzylpiperidin-1-yl] which showed IC50 of 0.024 μM in NMDA receptor assay. The compds. I are highly effective and selective antagonists of NMDA receptor, and moreover most of the compds. I are selective antagonist of NR2B subtype of NMDA receptor.

IT **420136-15-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of carboxamides as NMDA receptor antagonists)

RN 420136-15-8 CAPLUS

CN Piperidine, 1-[[6-(2-aminoethoxy)-1H-indol-2-yl]carbonyl]-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



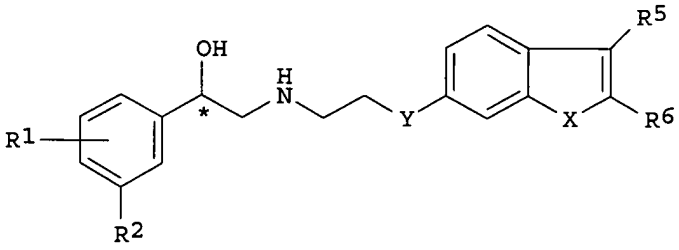
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:816638 CAPLUS
DOCUMENT NUMBER: 135:357839
TITLE: Preparation of bicyclic compounds such as benzofuran, indole, benzothiofuran, and indene derivatives of phenylethanolamine as β adrenoreceptor agonists
INVENTOR(S): Ikuta, Shunichi; Miyoshi, Shiro; Ogawa, Kohei
PATENT ASSIGNEE(S): Asahi Kasei Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083451	A1	20011108	WO 2001-JP3575	20010425
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001052574	A5	20011112	AU 2001-52574	20010425
CA 2407538	AA	20021025	CA 2001-2407538	20010425
EP 1277736	A1	20030122	EP 2001-925911	20010425
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003191174	A1	20031009	US 2002-258817	20021028
US 2004127546	A1	20040701	US 2004-761265	20040122

PRIORITY APPLN. INFO.:	JP 2000-130414	A	20000428
	WO 2001-JP3575	W	20010425
	US 2002-258817	A3	20021028

OTHER SOURCE(S): MARPAT 135:357839
GI



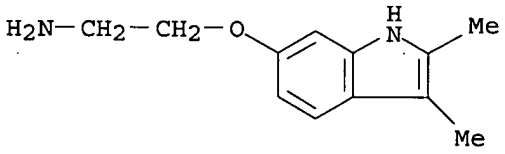
I

AB Compds. of the general formula (I) or salts thereof [wherein R1 is hydrogen, hydroxy, or halo; R2 is NHSO2R3, SO2NR4R4' (wherein R3 is C1-6

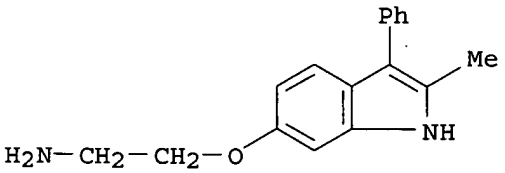
alkyl, benzyl, Ph, or NR4R4'; R4, R4' = H or C1-6 alkyl); R5 and R6 are each independently hydrogen, C1-6 alkyl, optionally substituted Ph, or benzyl; X is NH, sulfur, oxygen, or methylene; Y is oxygen, NR7, sulfur, methylene, or a bond (wherein R7 is H, C1-6 alkyl, or C1-6 acyl); and * represents an asym. carbon atom.] are prepared These compds. exhibit a potent and selective stimulating activity for human β3 adrenoreceptor with very little effect on increasing heart beat of guinea pigs and are useful as preventive and therapeutic drugs for diabetes, obesity, hyperlipidemia, digestive system diseases, depression, and urinary disorders. Thus, N-(3-bromoacetylphenyl)methanesulfonamide, 2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamine, and Et3N were added to DMF, stirred at room temperature for 1 h, treated with a solution of NaBH4 in ethanol, and stirred at room temperature for 5 h to give, after purification on a reversed phase column, N-[3-[2-[[2-(2,3-dimethyl-1H-indol-6-yloxy)ethyl]amino]-1-hydroxyethyl]phenyl]methanesulfonamide trifluoroacetate salt (II). II was as potent as isoproterenol for stimulating the production of cAMP in CHO cell line expressing human β3 adrenoreceptor (Ed50 of 8.7 nM).

IT **372093-05-5P**, 2-(2,3-Dimethyl-1H-indol-6-yloxy)ethylamine
372094-69-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicyclic compds. such as benzofuran, indole, benzothiofuran, and indoline derivs. of phenylethanolamine as β adrenoreceptor agonists and preventive and therapeutic drugs)

RN 372093-05-5 CAPLUS
CN Ethanamine, 2-[(2,3-dimethyl-1H-indol-6-yl)oxy]- (9CI) (CA INDEX NAME)



RN 372094-69-4 CAPLUS
CN Ethanamine, 2-[(2-methyl-3-phenyl-1H-indol-6-yl)oxy]- (9CI) (CA INDEX NAME)



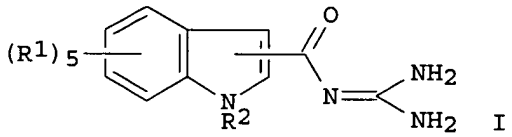
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:10088 CAPLUS
DOCUMENT NUMBER: 134:71491
TITLE: Indoloylguanidine derivatives useful as inhibitors of Na+/H+ exchanger activity.
INVENTOR(S): Kitano, Masahumi; Nakano, Kazuhiro; Yagi, Hideki; Ohashi, Naohito; Kojima, Atsuyuki; Noguchi, Tsuyoshi;

Miyagishi, Akira
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: U.S., 69 pp., Cont.-in-part of U.S. Ser. No. 230,223, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6169107	B1	20010102	US 1995-544292		19951017
US 6248772	B1	20010619	US 2000-604826		20000627
PRIORITY APPLN. INFO.:			JP 1993-125085	A	19930428
			US 1994-230223	B2	19940420
			JP 1994-280025	A	19941018
			US 1995-544292	A3	19951017

OTHER SOURCE(S): MARPAT 134:71491
GI



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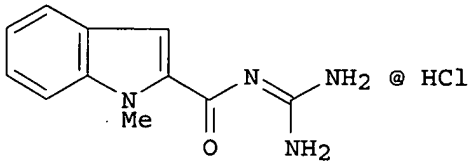
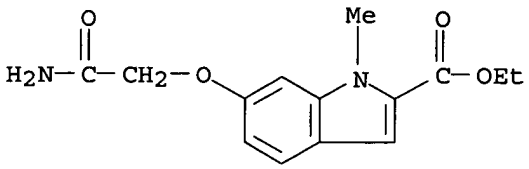


II

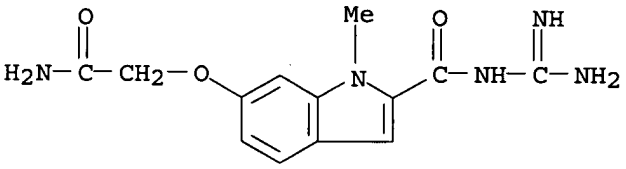
AB Indoloylguanidine derivs. I [R1 = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, halo, NO2, acyl, CO2H, alkoxycarbonyl, aromatic group, (un)substituted OH, NH2, SO2NH2, etc.; R2 = H, (un)substituted alkyl, cycloalkyl, OH, alkoxy, etc.] and their pharmaceutically acceptable acid addition salts inhibit Na+/H+ exchanger activity, and are consequently useful in the treatment or prevention of diseases caused by increased Na+/H+ exchanger activity. These include hypertension, arrhythmia, angina pectoris, cardiac hypertrophy, diabetes, disorders associated with ischemia or ischemic reperfusion, cerebro-ischemic disorders, and diseases caused by excessive cell proliferation. Over 250 synthetic examples and 22 precursor prepns. are given, with bioassay results for most invention compds. For example, condensation of Me 1-methyl-2-indolecarboxylate with guanidine HCl in the presence of NaOMe at ≤ 130° gave, after chromatog. and salification, 30.8% title compound II. In an assay for inhibition of ischemia-and-reperfusion-induced cardiac arrhythmia in rats, II at 0.3 mg/kg reduced mortality from 76% (control) to 0%, whereas EIPA [5-(N-ethyl-N-isopropyl)amiloride] reduced mortality to only 44% at the same dose.

IT **167479-34-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of indoloylguanidine derivs. as Na+/H+ exchanger inhibitors)

RN 167479-34-7 CAPLUS
CN 1H-Indole-2-carboxylic acid, 6-(2-amino-2-oxoethoxy)-1-methyl-, ethyl ester (9CI) (CA INDEX NAME)

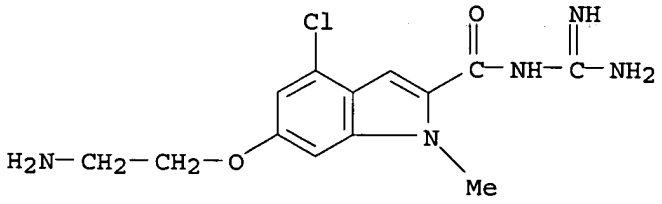


IT **178050-92-5P 178051-80-4P 178051-82-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indoloylguanidine derivs. as Na+/H+ exchanger inhibitors)
RN 178050-92-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-(aminoiminomethyl)-6-(2-amino-2-oxoethoxy)-1-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



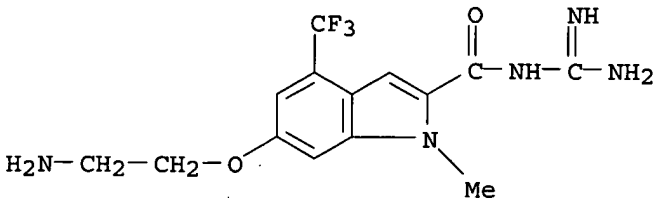
●2 HCl

RN 178051-80-4 CAPLUS
CN 1H-Indole-2-carboxamide, 6-(2-aminoethoxy)-N-(aminoiminomethyl)-4-chloro-1-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 178051-82-6 CAPLUS
CN 1H-Indole-2-carboxamide, 6-(2-aminoethoxy)-N-(aminoiminomethyl)-1-methyl-4-(trifluoromethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

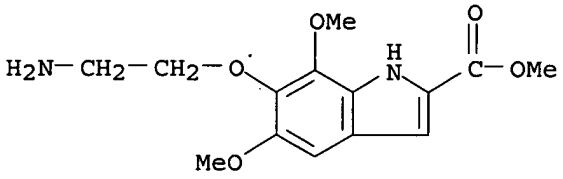
L4 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:697801 CAPLUS
DOCUMENT NUMBER: 134:136596
TITLE: Synthesis and HPLC analysis of enzymatically cleavable linker consisting of poly(ethylene glycol) and dipeptide for the development of immunoconjugate
AUTHOR(S): Suzawa, T.; Nagamura, S.; Saito, H.; Ohta, S.; Hanai, N.; Yamasaki, M.
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Asahi-machi, Machida-shi, Tokyo, 194-8533, Japan
SOURCE: Journal of Controlled Release (2000), 69(1), 27-41
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A model compound of antitumor agent, segment B of duocarmycin derivative DU-86, was conjugated to tumor-specific antibody via a cleavable linker consisting of poly(ethylene glycol) (PEG) and dipeptide, l-alanyl-l-valine (Ala-Val), to confirm the feasibility of the linker for application to immunoconjugate. The release of segment B from the linker was evaluated by HPLC anal. When segment B was derivatized to have an amino residue and then linked to PEG through a dipeptide, segment B was cleaved at the peptide bond by a particular enzyme, thermolysin (EC 3.4.24.4), but not by plasmin (EC 3.4.2 1.7), indicating that certain protease specifically expressed at the tumor site would be capable of peptide-specific digestion and release of anti-tumor agent since a thermolysin-like enzyme has been reported to be expressed at many tumor cells. Furthermore, the results showing that cell extract from G361 human melanoma had an ability to digest the linker peptide while the linker was stable in normal human serum suggested the tumor-specific activation of the conjugated agent. Segment B was conjugated via the linker to murine monoclonal antibody KM641 reactive to GD3 ganglioside to form immunoconjugate and the quant. release of segment B under the treatment with the enzyme was also confirmed. These results indicate the possibility of double targeting based on both the recognition ability of tumor specific antibody and tumor specific activation of the antitumor agents to enhance tumor treatment efficacy and to decrease unwanted side effects.

IT **185218-72-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and HPLC anal. of enzymically cleavable linker consisting of PEG and dipeptide for development of immunoconjugate)

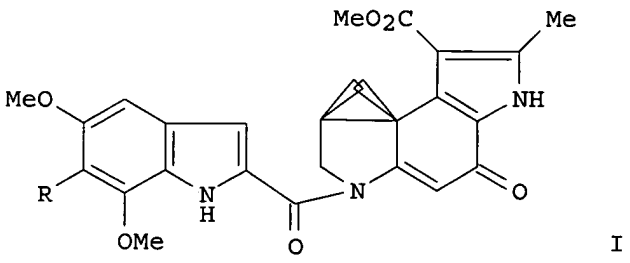
RN 185218-72-8 CAPLUS

CN 1H-Indole-2-carboxylic acid, 6-(2-aminoethoxy)-5,7-dimethoxy-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:564511 CAPLUS
DOCUMENT NUMBER: 133:335107
TITLE: Synthesis of a novel duocarmycin derivative DU-257 and its application to immunoconjugate using poly(ethylene glycol)-dipeptidyl linker capable of tumor specific activation
AUTHOR(S): Suzawa, T.; Nagamura, S.; Saito, H.; Ohta, S.; Hanai, N.; Yamasaki, M.
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd, Tokyo, 194-8533, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(8), 2175-2184
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Novel anti-tumor agent, duocarmycin derivative DU-257 [I; R = H2NCH2CH2O, (II)], was designed and synthesized to prepare immunoconjugate in order to confirm the feasibility of enzymically cleavable linker consisting of poly(ethylene glycol) (PEG) and dipeptide, L-alanyl-L-valine. Oxyethylamine arm was introduced at 4-methoxy position of segment B of DU-86 [I; R = OMe, (III)] to form II and evaluated its property. II retained similar stability and potency with III while enhanced hydrophilicity suggested. II was condensed to the PEG-dipeptidyl linker through carboxyl terminal of dipeptide, and enzymic release of II using a model enzyme, thermolysin, similar enzyme of which was shown to be overexpressed at various tumor sites, was evaluated by HPLC anal. Cleavage between the linker amino acids by the model protease and release of II as valine conjugated form was confirmed. The enzymically released

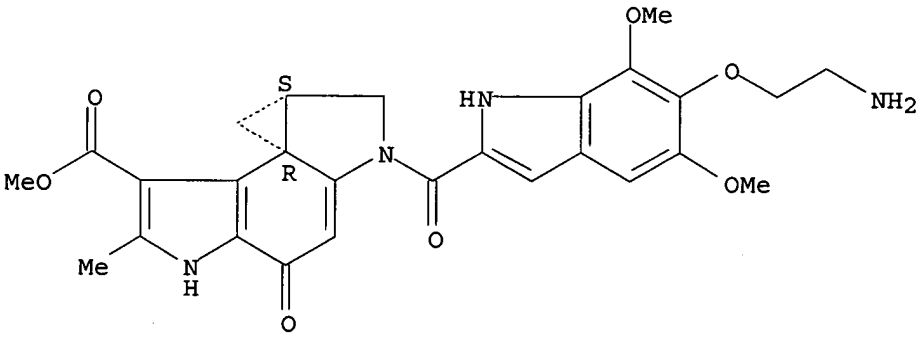
form of II expressed its cytotoxicity without loss of the potency for HeLaS3 and SW1116 tumor cell lines, although the efficacy was different in individual cells. II was then conjugated through the linker to KM231 monoclonal antibody specifically reactive to GD3 antigen which was shown to be expressed on the surface of many malignant tumors such as SW1116. The conjugate retained its binding specificity for SW1116 cell with a similar activity with KM231. Furthermore, the conjugate showed significant growth inhibition on SW1116 cell at a concentration of 75 μg/mL while no effect on antigen neg. cell, HeLaS3. These results suggest that the conjugate retained its anti-tumor effect only when it bound on and was activated at the target cell, simultaneously. II will be one of the candidate of anti-tumor agent for application to immunoconjugate and its conjugate with KM231 via PEG-dipeptidyl linker will be a useful entity for cancer therapy related to sLea expression.

IT **185218-65-9P**, DU 257
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of a novel duocarmycin derivative DU-257 and its application to immunoconjugate using poly(ethylene glycol)-dipeptidyl linker capable of tumor specific activation)

RN 185218-65-9 CAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[[6-(2-aminoethoxy)-5,7-dimethoxy-1H-indol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:44674 CAPLUS
DOCUMENT NUMBER: 126:65386
TITLE: Preparation of antitumor toxin complexes
INVENTOR(S): Suzawa, Toshiyuki; Yamasaki, Motoo; Nagamura, Satoru; Saito, Hiromitsu; Ohta, So; Hanai, Nobuo
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9635451	A1	19961114	WO 1996-JP1241	19960510
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2220339	AA	19961114	CA 1996-2220339	19960510
EP 867190	A1	19980930	EP 1996-913722	19960510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6103236	A	20000815	US 1997-981416	19971110
US 6638509	B1	20031028	US 2000-500243	20000208
PRIORITY APPLN. INFO.:			JP 1995-111933 A	19950510
			WO 1996-JP1241 W	19960510
			US 1997-981416 A3	19971110

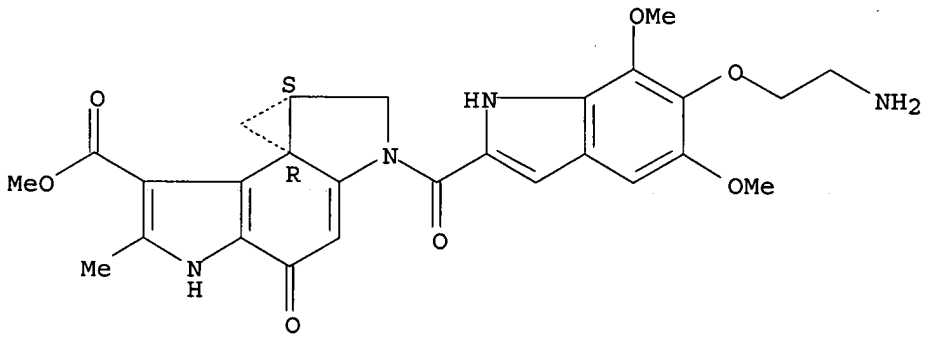
AB A toxin complex is prepared by bonding a residue of a compound having target cell affinity and a residue of toxin via a spacer containing a polyalkylene glycol and a dipeptide. The compds. which show cell affinity include tumor-specific antibody and its fragments. For example, HO-PEG-Ala-Val-adriamycin reaction products with NL-1 (acute lymphocytic leukemia antibody) was prepared and its antiproliferative effect against Daudi Burkitt's lymphoma cells was tested.

IT **185218-65-9DP**, reaction products with PEG-Ala-Val-OH derivative and antibody
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor toxin complex via spacer containing polyalkylene glycol and dipeptide)

RN 185218-65-9 CAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[[6-(2-aminoethoxy)-5,7-dimethoxy-1H-indol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

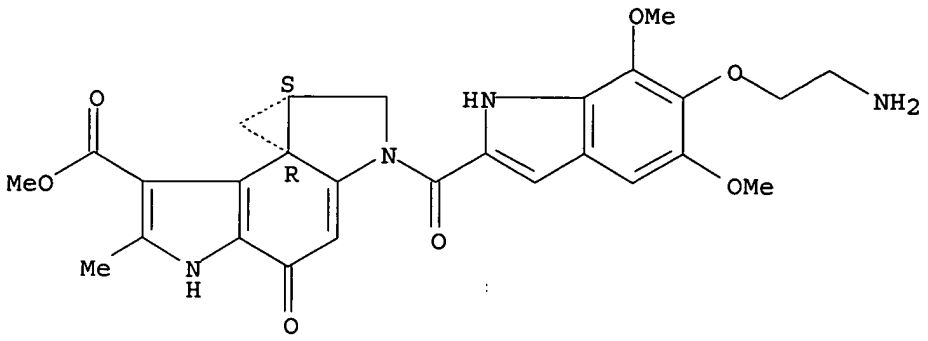


IT **185218-65-9P 185218-72-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antitumor toxin complex via spacer containing polyalkylene glycol and dipeptide)

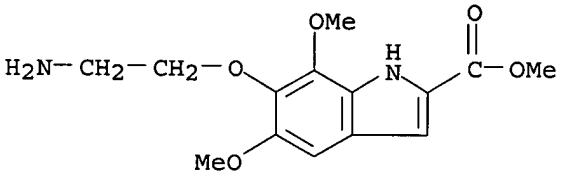
RN 185218-65-9 CAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[[6-(2-aminoethoxy)-5,7-dimethoxy-1H-indol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



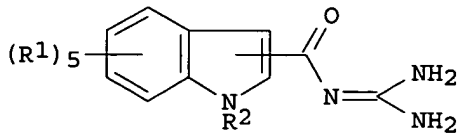
RN 185218-72-8 CAPLUS
CN 1H-Indole-2-carboxylic acid, 6-(2-aminoethoxy)-5,7-dimethoxy-, methyl ester (9CI) (CA INDEX NAME)



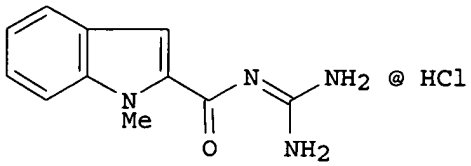
L4 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:379686 CAPLUS
DOCUMENT NUMBER: 125:58312
TITLE: Indoloylguanidine derivatives useful as inhibitors of Na+/H+ exchanger activity.
INVENTOR(S): Kitano, Masahumi; Nakano, Kazuhiro; Yagi, Hideki; Ohashi, Naohito; Kojima, Atsuyuki; Noguchi, Tsuyoshi; Miyagishi, Akira
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Company, Limited, Japan
SOURCE: Eur. Pat. Appl., 99 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 708091	A1	19960424	EP 1995-307409	19951018
EP 708091	A3	19960717		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
JP 08208602	A2	19960813	JP 1995-286772	19951006
CA 2160600	AA	19960419	CA 1995-2160600	19951016
CN 1136038	A	19961120	CN 1995-116169	19951017
CN 1067988	B	20010704		
TW 386991	B	20000411	TW 1995-84110984	19951018
PRIORITY APPLN. INFO.:			JP 1994-280025 A	19941018
OTHER SOURCE(S):	MARPAT 125:58312			

GI



I



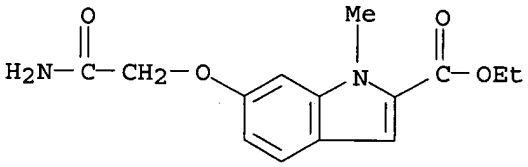
II

AB Indoloylguanidine derivs. I [R1 = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, halo, NO2, acyl, CO2H, alkoxycarbonyl, aromatic group, (un)substituted OH, NH2, SO2NH2, etc.; R2 = H, (un)substituted alkyl, cycloalkyl, OH, alkoxy, etc.] and their pharmaceutically acceptable acid addition salts inhibit Na+/H+ exchanger activity, and are consequently useful in the treatment or prevention of diseases caused by increased Na+/H+ exchanger activity. For example, condensation of Me 1-methyl-2-indolecarboxylate in the presence of NaOMe at ≤ 130° gave, after chromatog. and salification, 30.8% title compound II. In an assay for inhibition of ischemia-and-reperfusion-induced cardiac arrhythmia in rats, II at 0.3 mg/kg reduced mortality from 76% (control) to 0%, whereas EIPA [5-(N-ethyl-N-isopropyl)amiloride] reduced mortality to only 44% at the same dose.

IT **167479-34-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of indoloylguanidine derivs. as Na+/H+ exchanger inhibitors)

RN 167479-34-7 CAPLUS

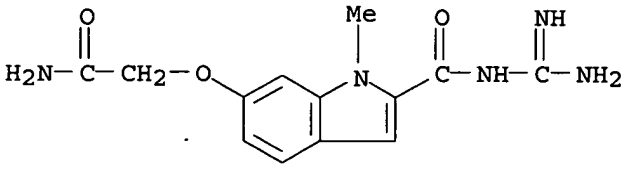
CN 1H-Indole-2-carboxylic acid, 6-(2-amino-2-oxoethoxy)-1-methyl-, ethyl ester (9CI) (CA INDEX NAME)



IT **178050-92-5P 178051-80-4P 178051-82-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indoloylguanidine derivs. as Na+/H+ exchanger inhibitors)

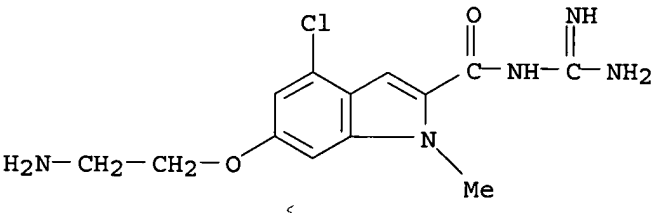
RN 178050-92-5 CAPLUS

CN 1H-Indole-2-carboxamide, N-(aminoiminomethyl)-6-(2-amino-2-oxoethoxy)-1-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



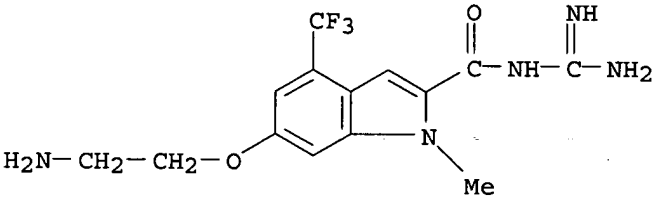
●2 HCl

RN 178051-80-4 CAPLUS
CN 1H-Indole-2-carboxamide, 6-(2-aminoethoxy)-N-(aminoiminomethyl)-4-chloro-1-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 178051-82-6 CAPLUS
CN 1H-Indole-2-carboxamide, 6-(2-aminoethoxy)-N-(aminoiminomethyl)-1-methyl-4-(trifluoromethyl)-, dihydrochloride (9CI) (CA INDEX NAME)



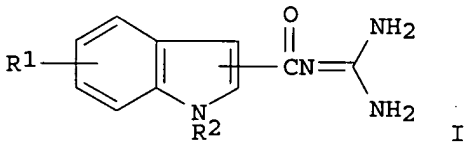
●2 HCl

L4 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:781759 CAPLUS
DOCUMENT NUMBER: 123:169498
TITLE: Indoloylguanidine derivatives as inhibitors of sodium-hydrogen exchange.
INVENTOR(S): Kojima, Atsuyuki; Kitano, Masahumi; Miyagishi, Akira; Noguchi, Tsuyoshi; Yagi, Hideki; Nakano, Kazuhiro; Ohashi, Naohito
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 60 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 622356	A1	19941102	EP 1994-303101	19940428
EP 622356	B1	19980701		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
JP 07010839	A2	19950113	JP 1994-99363	19940412
JP 3162572	B2	20010508		
CA 2121391	AA	19941029	CA 1994-2121391	19940415
TW 402600	B	20000821	TW 1994-83103505	19940420
CN 1106800	A	19950816	CN 1994-105367	19940428
CN 1051301	B	20000412		
AT 167854	E	19980715	AT 1994-303101	19940428
ES 2117759	T3	19980816	ES 1994-303101	19940428

PRIORITY APPLN. INFO.: JP 1993-125085 A 19930428
OTHER SOURCE(S): MARPAT 123:169498
GI



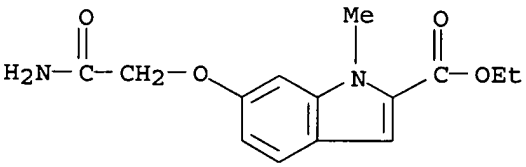
I

AB The title compds., N-(diaminomethylene)-1H-indolecarboxamides (indoloylguanidines) I (R1 = H, alkyl, alkenyl,etc.; R2 = H, alkyl, cycloalkyl, etc.) were disclosed as compds. that inhibit the Na+/H+ exchanger activity and are therefore useful in the treatment and prevention of disease caused by increased Na+/H+ exchanger activity.

IT **167479-34-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of sodium channel blocker N-([(dimethylamino)methylene]indolecarboxamide)

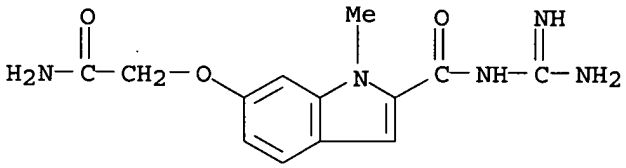
RN 167479-34-7 CAPLUS

CN 1H-Indole-2-carboxylic acid, 6-(2-amino-2-oxoethoxy)-1-methyl-, ethyl ester (9CI) (CA INDEX NAME)



IT **167477-92-1P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sodium channel blocker N-([(dimethylamino)methylene]indoleca

rboxamide)
RN 167477-92-1 CAPLUS
CN 1H-Indole-2-carboxamide, N-(aminoiminomethyl)-6-(2-amino-2-oxoethoxy)-1-methyl-, hydrochloride (9CI) (CA INDEX NAME)



● x HCl

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	42.31	203.85

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.84	-5.84

STN INTERNATIONAL LOGOFF AT 15:27:55 ON 25 JAN 2005